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1647

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Barbara A. Gilchrest, Mina Yaar and Mark Eller		
Application No.:	09/018,194	Group:	1647
Filed:	February 4, 1998	Examiner:	S. L. Wegert
Confirmation No.:	9447		
For:	Inhibition of Apoptosis in Keratinocytes by a Ligand of p75 Nerve Growth Factor Receptor (As Amended)		

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Beverly Weinberger
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INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A telephonic interview was conducted on March 25, 2004. Participants were:

Examiner Sandra Wegert

Examiner Elizabeth Kemmerer

Inventor Barbara A. Gilchrest

Inventor Mina Yaar

Attorney Doreen M. Hogle

Attorney Carol A. Egner

The attorneys and inventors wish to thank the Examiners for holding the interview.

Arguments were presented that pertained to all the claims currently under examination. No new exhibits or new Declarations were presented. Examiner Sandra Wegert was sent by fax

an informal paper, not to be entered, "Points to Consider for Telephonic Interview," preceding the interview.

No prior art was discussed, as the one remaining rejection is under 35 U.SC.§ 112, first paragraph.

Points Presented at Interview Relative to Enablement of the Claims

Keratinocytes either go into producing hair shaft or go into producing the stratum corneum. Keratinocytes in culture can be used to predict the behavior of keratinocytes in skin. The intracellular pathways the keratinocytes use to differentiate are the same. The apoptosis (cell death) pathways are the same for keratinocytes, whether they are in stratum corneum or in hair follicles. If the apoptotic pathway is blocked in keratinocytes, cell death is prevented, whether the keratinocytes are in stratum corneum or in hair follicles.

There are many factors affecting hair growth and those factors and their possible interactions are poorly understood. Despite the complexity, modulating one pathway can have an effect. Although the observed effect may not be absolute, and may not be a "cure" for hair loss, an observed effect on maintaining hair or slowing loss is nevertheless valued.

Male pattern baldness is not permanent hair loss. Rather, it is a phenomenon that results from a shift in the relative lengths of the phases of hair growth, anagen (growth), catagen (regression) and telogen (rest). In male pattern baldness, anagen is not long enough, resulting in only short, fine hairs. Therefore, an agent that changes the length of the phases of hair growth will have an effect on male pattern baldness.

Alopecia areata is real hair loss that occurs by an immunological mechanism. An infiltrate of T lymphocytes surrounds the keratinocytes, causing catagen.

UV irradiation of keratinocytes in cell culture is not meant to mimic, and does not mimic, the factors that contribute to male pattern baldness or to alopecia areata. Rather, UV is used only as an initiating event for apoptosis. In the model of hair loss using UV on cells in culture, the radiation is brief -- only long enough to activate pathways for the cells to commit suicide. The

p75 pathway is a common final pathway to cause apoptosis, found in all cells. UV is not the relevant stimulus that causes male pattern baldness, but sets in motion pathways going through the p75 receptor. The p75 receptor governs transitions of anagen through telogen. Applicants' method blocks the transition to catagen.

The experiments described in the Declaration of Barbara A. Gilchrest, M.D. Under 37 C.F.R. § 1.132, mailed to the United States Patent and Trademark Office on April 8, 2002, were reviewed. It was noted during the interview that experiments were performed on biopsies of mouse skin maintained in organ culture during the early stages of catagen. Cyclic peptide SEQ ID NO:9 (CATDIKGAEC) or diluent was added to the mouse organ explants as control. The cyclic peptide delayed catagen development of hair, showing that blocking neurotrophin receptor p75 activation is associated with delay of catagen initiation.

More recent experiments are consistent with these results. [See the attached abstract, labeled "Appendix," referred to by Dr. Gilchrest, but not presented at the time of the interview: Zhai S., Yaar M., Reenstra W., Gilchrest B.A. Elucidation of apoptotic pathways following activation of the 75 kDa neurotrophin receptor. *J. Invest. Dermatol. 112*:548, 1999 (Abstract 151).]

Examiner Wegert pointed out that the language in the claims -- Claim 33, for example -- is to maintaining hair growth, and suggested that what is observed from the experiment described in the Declaration is perhaps more accurately "delaying catagen" or "delaying hair loss." Applicants were invited to submit additional claims with alternative claim language.

Respectfully submitted,
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Dated: April 23, 2004

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Elucidation of Apoptotic Signaling Pathways Following Activation of the 75 kDa Neurotrophin Receptor

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The 75 kDa neurotrophin receptor (p75) is strongly expressed in keratinocytes, melanocytes and neurons and has been implicated in apoptosis of these cells under certain conditions. When neurotrophins activate p75 together with receptors of the Trk family, p75 evokes a survival signal. However, when p75 is activated alone, it may signal for apoptosis by stimulating within minutes sphingomyelin turnover and ceramide generation. Still, the sequence of events linking p75 stimulation to ceramide generation and apoptosis remain largely unknown. To investigate p75 early signaling, NIH-3T3 cells engineered to constitutively express human p75 (3T3-p75), were stimulated with a known p75 ligand β amyloid (βA), and the distribution of p75 on the cell surface was analysed using immunohistochemistry and confocal laser microscopy. Within minutes βA-treated cultures displayed aggregation of p75, while the baseline, homogeneous cell surface distribution of p75 did not change in diluent treated cultures. Furthermore, 3T3-p75 stimulated with βA in the presence of a bifunctional crosslinker and then reacted with anti p75 antibodies displayed on western blots in addition to the expected 75 kDa band also a ~220–230 kDa band, consistent with receptor trimerization, as reported for other apoptotic signaling pathways. Moreover, similar to signaling initiated by the apoptotic TNF-α and Fas receptors, βA activation of p75 strongly induced the transcription of the immediate early *c-jun* mRNA, stimulated the stress-activated c-Jun NH_2-terminal kinase (JNK) as measured by phosphorylation of its substrate [GST-cJun (1–79)], activated caspase-3 to cleave its substrate [poly (ADP ribose)polymerase], and induced the characteristic DNA fragmentation into multimers as measured by TUNEL analysis and DNA ladder formation. To determine if the initial step of p75 aggregation is required for initiation of apoptosis, 3T3-p75 were pretreated with an HPLC purified cyclic peptide (CATDIKGAEC) that binds the ligand binding site of p75, and then cultures were stimulated with βA or with diluent alone. The cyclic peptide inhibited p75 aggregation, decreased *c-jun* mRNA induction, reduced GST-cJun (1–79) phosphorylation, and suppressed cellular apoptosis. The universality of the pathway was confirmed by treating UV-irradiated keratinocytes (50 mJ per cm^2, metered at 285 ± 5) with the cyclic peptide. Cyclic peptide blocking of p75 decreased *c-jun* transcription that was otherwise prominent in UV-irradiated diluent-treated keratinocytes. Our data identify for the first time the initial signaling events that follow p75 activation and suggest that signaling through p75 requires receptor aggregation. Hence, p75 mediated apoptosis could be abrogated by cyclic peptides that isolate the receptor, preventing its activation.

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The Human Nude Phenotype: Congenital Alopecia and Severe T
Associated with a Nonsense Mutation in the Whn Gene

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University, New York, New York

The nude mouse phenotype is characterized by congenital absence of
deficiency, resulting from mutations in the *whn* gene (*winged-helix-*
forkhead winged helix transcription factor family member with restric
and skin. Identification of the human counterpart of the nude mutati
presumably because affected individuals succumb to the immunodefici
absence of hair can be appreciated. Recently, the simultaneous occurren
cell immunodeficiency, congenital alopecia and nail dystrophy (MIN
siblings from a consanguineous Italian family was reported. One siblin
marrow transplantation which corrected the immunodeficiency, but no
We sought to test the hypothesis that this syndrome represented a candid
mutations in the human *whn* gene. We found suggestive evidence of li
human chromosome 17 (Z_{max} = 1.32), identified a homozygous non
individuals, and localized the expression of human *whn* to tissues involv
findings implicate a forkhead winged helix family member in the
developmental defects as congenital absence of the hair and athymia in

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Agouti Signaling Protein Inhibits Melanogenesis Primarily by Binding to the Melanocortin-1 Receptor

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Agouti signaling protein (ASP) is known to antagonize the melanogenic effects of α-melanocyte stimulating hormone (α-MSH) on mouse follicular melanocytes, resulting in the switch from eumelanin to pheomelanin synthesis. We have shown that ASP completely abrogates the mitogenic

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Glucocorticoids Induce a Near-Total Suppression of Hyaluronan Sy
Fibroblasts and in Osteoblasts: A Molecular Mechanism Contributing

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of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania

Topical and systemic glucocorticoids induce an atrophy of skin, bon
characterized by decreased tissue content of glycosaminoglycans, in
-HAs. We took advantage of the recent cloning of the three mamm
-HASs enzymes, HAS-1, -2, and -3, to explore the molecular basis o
blots performed on RNA extracted from cultured dermal fibroblasts

Appendix